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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,627	04/14/2004	Renata Pasqualini	UTSC:858US	6275

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,627	PASQUALINI ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/04, 1/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-39 are presently pending and under examination.

Specification

2. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

3. The use of the trademarks IMMORTOMOUSE and XENOMOUSE have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 8 and 25-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 8 recites that the cells are cultured in "hybridoma culture medium" however there does not appear to be a definition provided in the specification that would inform the skilled

artisan as to what was intended by this limitation. Thus, the skilled artisan would be unable to determine the metes and bound of this limitation.

7. Claim 25 recites a method where steps "(a)", "(c)", and "(b)" are carried out. As theses steps are not listed in appropriate order, the skilled artisan could potentially be deceived as to what order the steps were to be performed in. As such the metes and bounds of this claim and any claim which depends from this claim can be properly determined.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 24 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification provides no detail regarding the administration of antibody to a subject in need. In order to carry out the claimed invention, the skilled artisan would be forced to undertake an undue level of experimentation.

10. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and

the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. Each of claims 24 and 39 is drawn to a further step of the antibody production methods wherein the antibodies that are produced are administered to a subject in need of the antibodies. As there has been no limitation placed as to what antigen these antibodies might be directed against, both claims are very broad in their subject matter. Any antibody produced by the method of the invention can be used for administration to a subject in need, which would necessarily comprise any disease that an antibody therapy may potentially be useful.

12. Antibody therapies have indeed been used in the past, however the successful application of any antibody in a therapy setting requires a high level of experimentation aside from simply producing the antibody. Aside from identifying appropriate antibodies, one must carefully ascertain what dosage of the antibody will be effective in treating the disease of interest, without leading to harmful side effects, such as immune complex deposition in the kidneys. This is an unpredictable level of necessary information as different antibodies have different binding affinities for their cognate antigen and thus will respond differently in an *in vivo* environment.

13. Indeed Chester (Tumor Biol 25: 91-98 (2004), newly cited) teaches that the development of antibody-based therapeutics requires a high level of non-routine experimentation.

> The scope of knowledge required to develop antibody-based therapeutics is broad as shown in figure 1, which illustrates the transitional cycle from laboratory to clinic with feed back from the clinic to the laboratory for further development. The data elements needed for these processes require knowledge of: tumor pathophysiology, accessible and tumor-specific targets for therapy, structure and function of antibodies, distribution of antibodies and their metabolism in man, design of antibodies to deliver therapy effectively, production, testing in animal models, clinical trials, and use of preclinical and clinical data to inform further laboratory research.
>
> (page 92, first full paragraph)

It is thus clear that a high level of experimentation is required in order to successfully establish a therapeutic protocol for an antibody.

14. From this one must then ask what level of instruction is provided in the specification to enable the skilled artisan to carry out the invention. In short, the specification provides little information aside from the method for producing the antibodies in the absence of hybridoma formation. There is no discussion of proper dosages or even appropriate targets that may be useful. Thus, the skilled artisan would be forced to carry out a high level of experimentation that would included, but not be limited to, identifying appropriate targets for antibody-mediated therapeutic intervention, determining effective levels of affinity, and determining what dosages would give an efficacious result. It is thus clear, that to carry out the methods as claimed in claims 24 and 39, the skilled artisan would be required to perform an undue level of burdensome experimentation. Therefore, the specification does not enable the skilled artisan to carry out the invention as claimed.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1, 11-16, and 19-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Harlow (Antibodies: A Laboratory Manual (1988), of record). The claims are drawn to a method for generating antibody-producing cells by contacting an antibody-producing cell, which is

capable of being immortalized without hybridoma formation, and immortalizing the cell. Note that the cell only need be "capable" of forming an immortal cell. There is no active step recited whereby a hybridoma is not formed, i.e. there is no step specifying that an oncogene is responsible for the immortalization step. It is also noted that any cell is "capable" of becoming immortalized as at the step of crisis or senescence, a certain proportion of cells indeed become immortalized. Thus, any B cell is necessarily capable of becoming immortalized.

17. Harlow teaches the well-known process of forming hybridomas that are stable antibody-producing cells. Each of the remaining claims simply recites methods that are well known in the art, each of which is taught by Harlow.

18. Claim 1, 14, 15, 19, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kano (JP62195296, of record). Kano discloses a method of immortalizing an antibody-producing cell by immunizing an animal against an antigen, then isolating spleen cells and immortalizing the cells by insertion of an oncogene.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 1, 11-16, and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow in view of Lichtman (Nature 324: 489-491 (1986), newly cited). Harlow discloses the well-known processes of immunizing mice, isolating the appropriate B cells an

immortalizing them. Harlow however teaches the common procedure of hybridoma production in order to immortalize the antibody-producing B cells. Thus, Harlow does not teach the immortalization of antibody-producing B cells using an oncogene.

21. Lichtman teaches that murine lymphocytes specific for an antigen can indeed be immortalized by an oncogene, namely a Kirsten Sarcoma Virus delivered ras gene.

22. One would have been motivated to immortalize the antibody-producing cells of Harlow using the methods of Lichtman because the methods of Lichtman avoid the hazards of hybridoma formation. Therefore it would have been obvious to one of ordinary skill in the art to immortalize the antibody-producing, antigen-specific B cells of Harlow using the methods of Lichtman.

23. Claims 1 and 11-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow and Lichtman as applied to claims 1, 11-16, and 19-23 above, and further in view of Green (J Immunol Meth 231: 11-23 (1999), newly cited). Harlow and Lichtman teach each of the limitations as described above, but do not specifically teach the use of transgenic mouse for immunization. Green teaches of a transgenic mouse that expresses only human antibody molecules and thus produces rearranged human antibodies upon immunization of the mouse. One would have been motivated to use the mouse as taught by Green for the production of antibodies as taught in combination by Harlow and Lichtman because: "The utility of the XENOMOUSE strains for the generation of large panels of high-affinity, fully human mAbs can be made available to researchers in the academic and private sectors, and should accelerate the development and application of mAbs as therapeutics for human disease" (Green, last line of abstract). Therefore it would have been obvious to one of ordinary skill in the art to have made

the antibody producing cells of Harlow and Lichtman using the mice taught by Green because human antibodies are much closer to clinical application than standard mouse monoclonals.

24. Claims 1-17, 19-23, and 25-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow in view of Jat (Proc Natl Acad Sci USA 88: 5096-5100 (1991), of record), as evidenced by Kano and Kanki (Hybridoma 13: 327-330 (1994), newly cited). The claims are drawn to a method of producing an antibody-producing cell with a conditional oncogene which can be a temperature sensitive SV40 large T antigen (TAg), which can be the A58S mutant allele of TAg, where the cells are produced at between 25°C and 35°C, ideally at 33°C.

25. Harlow teaches all of the standard procedures for immunizing mice, isolating the spleen cells, culturing the cells, assessing the antibody production after immortalization, producing monoclonal antibodies through limiting dilution, and producing polyclonal antibodies in the absence of single cell cloning. Harlow does not teach immortalization of the antibody-producing cells in the absence of hybridoma formation with no mention of temperature sensitive TAg.

26. Jat teaches a transgenic mouse comprising the A58S SV40 TAg allele providing conditionally immortal cells In order to derive these immortal cell lines the permissive temperature for growth is 33°C. Jat teaches that immortalized skin fibroblasts and thymic stromal cells are successfully produced from these mice. Indeed Jat asserts that "the use of fibroblast populations can be transferred readily to other cell systems" (page 5096, second column).

27. One would have been motivated to use the transgenic mice of Jat in the antibody production protocols of Harlow because the establishment of immortalized cell lines from the mouse of Jat is a simple procedure of culturing the cells at the permissive temperature. The skilled artisan would have reasonably expected the mice of Jat to lead to the production of stable

antibody-producing cells in the absence of hybridoma formation because Kano had taught that an oncogene could indeed lead to the immortalization of a stable antibody-producing cell, and Kanki had taught that the SV40 early region, which comprises TAg, could indeed immortalize B cells. Therefore, it would have been obvious to one of ordinary skill in the art to produce antibodies and antibody-producing cells in the mice of Jat in order to form antibody-producing cells in the absence of hybridoma formation.

28. Claims 1-23 and 26-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow, Jat, Kano, and Kanki as applied to claims 1-17, 19-23, and 25-38 above, and further in view of Green. Harlow, Jat, Kano, and Kanki teach each of the limitations as described above, but do not teach the use of a mouse comprising the genetic complement for producing human antibodies. Green teaches the XENOMOUSE which allows for the production of human monoclonal antibodies from a mouse. As argues above one would have been motivated to use an equivalent to the XENOMOUSE in the production of monoclonal antibodies, due to advantages related to clinical application. The skilled artisan would have readily recognized the need to interbreed the XENOMOUSE to the mouse of Jat in order to produce a mouse that could produce human antibodies, and produce immortalized B cell clones in the absence of hybridoma formation. Therefore, it would have been obvious to one of ordinary skill in the art to use a mouse transgenic both in the production of human antibodies, and transgenic for the temperature sensitive allele of TAg in order to produce antigen-specific B cells, through the combined teachings of Harlow, Jat, Green, Kano, and Kanki.

Conclusion

29. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Each of Kumar (Immunol Lett 65: 153-159 (1999) newly cited), Kempkes (Proc Natl Acad Sci USA 92: 5875-5879 (1995), newly cited), and Gorny (Proc Natl Acad Sci USA 86: 1624-1628 (1989), newly cited) is cited to show that the immortalization of B cells using oncogenes is a well-recognized method.

30. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

JAMES KETTER
PRIMARY EXAMINER